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FOR: PHARMACEUTICAL COMPOSITION CONTAINING A SMALL OR MEDIUM SIZE PEPTIDE

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Dear Sir or Madam:

Applicant, by its attorneys hereby submits to the USPTO a certified copy of the following application(s) which forms the basis of applicant's claim to priority.

Country: European Patent Convention

Application No. (s): 00102429.8

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Respectfully submitted,

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Patentanmeldung Nr. Patent application No. Demande de brevet n°

00102429.8

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

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PHARMACEUTICAL COMPOSITION CONTAINING A SMALL OR MEDIUM SIZED PEPTIDE

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition containing a small or medium sized peptide, free from preservatives and anyway stable before and during the use.

STATE OF THE ART

A remarkable number of peptides, derivatives and analogues thereof are known in therapy. They are often endowed with an utterly powerful biologic activity, therefore even very small amounts are required for therapeutic goals. Among these, small and medium sized peptides, such as, for example, analogues and derivatives of oxitocin and vasopressin, such as desmopressin (1-deamino-8-D-arginin-vasopressin), a powerful antidiuretic useful in the treatment of urinary disorders associated to, for example, insipidus diabetes and nocturnal enuresis.

The patent application WO 95/01185 (in the name of Ferring AB) claims a pharmaceutical composition for administering peptides, such as desmopressin, containing a buffer, a quaternary amine as preservative or disinfectant, and an agent for controlling the osmotic pressure. Besides the preservative or disinfectant activity already cited, the quaternary amine is capable of preventing the active principle to be adsorbed by the walls of the composition container, especially when these walls are of polymeric material. In fact, Example 5 shows that desmopressin solutions free from preservative lose about the half of active principle because of the adsorption by the walls of polystyrene, polypropylene and glass tubes, after 24 hours at room temperature.

The preferred quaternary amine according to WO 95/01185 is benzalkonium chloride. Recently, Hofmann T. et al., Springer-Verlag, 1998, 46:146-151 reported that this preservative causes the irreversible suppression of the nasal ciliar motility, such that its banning from the formulations for nasal administration is suggested.

The patent application WO 95/01183 (in the of Ferring AB) discloses a composition for the nasal administration of desmopressin. Though claim 1 does not report the presence of specific excipients, it is apparent from the description

and the examples that such composition always contains a preservative such as chlorobutanol or benzalkonium chloride.

SUMMARY OF THE INVENTION

It has been now surprisingly found that pharmaceutical compositions containing a small or medium seized peptides and free from preservatives not only are suitably stable, likewise analogous compositions containing this kind of additive, but also do not show the problem of the adsorption of the active principle by the walls of the container, envisaged by the prior art.

DESCRIPTION OF THE INVENTION

The present invention relates to a pharmaceutical compositions containing a therapeutically effective amount of a small or medium sized peptide in aqueous solution, characterized in that it is free from preservatives.

The peptide of the composition of the present invention is preferably selected from the group consisting of derivatives and analogues of oxitocin and vasopressin such, as, for example, terlipressin [(N-α-triglycin-8-lysin)-vasopressin], carbetocin [(1-desamino-1monocarba-2(O-methyl)tyrosine)-oxitocin], triptorelin (6-D-tryptophan-LH-RH) and desmopressin (1-deamino-8-D-arginin-vasopressin), and the salts thereof. Particularly preferred for the aim of the present invention are the vasopressin analogues, desmopressin acetate hydrate being the most preferred.

In a preferred embodiment, the composition of the present invention has a pH comprised between 3.5 and 6. For maintaining such a pH value the composition shall contain a suitable buffer such as, for example, citric acid /disodium phosphate dihydrate or citric acid/trisodium citrate dihydrate.

The composition of the present invention may also contain an agent for controlling the osmolarity such as, for example, sodium chloride.

In a preferred embodiment, the composition of the invention contains at least 0.02 mg of desmopressin, at least 3 mg of a buffer, an amount of agent for controlling the osmolarity such as the osmolarity is maintained to the physiologic values of the human plasma, and 1 ml of purified water.

Preferably the composition of the present invention contains from 3 to 6 mg of the citric acid/disodium phosphate dihydrate buffer, or from 5 to 11 mg of the citric acid/trisodium citrate dihydrate buffer.

More preferably, the composition of the present invention contains from 0.02 to 0.15 mg of desmopressin, preferably 0.1 mg, from 1 to 2.5 mg of citric acid monohydrate, preferably 1.7 mg, from 2 to 5 mg of disodium phosphate dihydrate, preferably 3 mg, 1 ml of water and an amount of sodium chloride such that the osmolarity is kept at the physiological values of the human plasma.

The advantages provided by the composition of the present invention over the prior art compositions are apparent. The possibility of avoiding the use of preservatives has a positive rebound from the toxicological point of view as these substances – and the case of benzalkonium chloride is epitomising – are often a source of allergic and irritative reactions from the mucosae. Furthermore the present composition represents an overcoming of a prior art prejudice attesting that desmopressin solutions free from preservatives have the drawback of suffering an adsorption process of the active principle by the container walls. As it is demonstrated below, the composition of the invention, though free from preservatives, does not show such an drawback.

The composition of the present invention is prepared in pre-sterile environment and sterilely filtered through 0,22 μm filters.

This is administered by a spray device filled in sterile environment under nitrogen. The vial of the spray device is preferably of glass. Such device is equipped with a multidose pump of a kind allowing the prevention of the bacterial contamination of the drug solution, before and during the use, thanks to the protection of the aspiration air by an absolute filter and an auto-blocking mechanism of the actuator. An example of a spray device of this kind is that described by the patent application EP 0 815 946 (in the name of Pfeiffer GmbH Erich).

Examples of accomplishment of the present invention will be now provided.

EXAMPLE 1

Solution at pH 5

Desmopressin acetate hydrate	0.1 mg
(equal to desmopressin base)	(89 μg)
Citric acid monohydrate	1.7 mg
Disodium phosphate dihydrate	3.0 mg
Sodium chloride	7.5 mg
Purified water	1 ml

EXAMPLE 2

Solution at pH 4

Desmopressin acetate hydrate	0.1 mg
(equal to desmopressin base)	(89 μg)
Citric acid monohydrate	4.64 mg
Trisodium citrate dihydrate	4.6 mg
Sodium chloride	6.8 mg
Purified water	1 ml

EXAMPLE 3

Evaluation of the adsorption of the active principle by the container walls

The compositions of Examples 1 and 2 were put in glass containers closed with a polymeric material pump, at room temperature for 4 days, and the titer in active principle was then evaluated.

The results are set forth in the following Table 1.

Table 1

Composition	Titer at time zero	Titer after 4 days
Example 1	108.5%	106.9%
Example 2	103.3%	101.5%

The results set forth by the table above clearly show that for both the compositions the adsorption process of the active principle on the glass and the polymeric material pump is negligible..

EXAMPLE 4

Stability test

The quality attributes required for the compositions of the present invention are the following:

Parameter	Attribute
pH	3.5-6.0
Desmopressin acetate hydrate	90-110 μg/ml
Microbiological quality	sterile

The compositions of the present invention were evaluated by stability tests in type I glass vials equipped with dispenser pump.

The applied test protocols were the following:

Real time test

It was carried out at a temperature of 5°C±3°C according to the scheme of Table 2.

Table 2

Test	Beginning	3 months	6 months	12 months	18 months
pH	X	X	X	X	X
Desmopressin acetate hydrate	X	X	X	X	X
Microbiological quality	X	-	-	-	X

The results are set forth in the following Tables 3 and 4

Table 3

(composition of Example 1)

Test	Beginning	3 months	6 months	12 months	18 months
pH	5.12	5.16	5.14	5.10	5.15
Desmopressin acetate hydrate	108.3%	107.6%	106.4%	107.1%	104.7%
Microbiological quality	Sterile	-	-	-	Sterile

Table 4

(composition of Example 2)

Test	Beginning	3 months	6 months	12 months	18 months
pH	4.00	4.00	4.00	3.98	4.02
Desmopressin acetate hydrate	109.0%	108.1%	108.8%	107.7%	106.0%
Microbiological quality	Sterile	-	-	-	Sterile

Room temperature tests

They were carried out at a temperature of 25°C±2°C and 60%±5% of relative humidity according to the scheme of Table 5

Table 5

Test	Beginning	3 months	6 months	12 months	18 months
pH	X	X	X	X	X
Desmopressin acetate hydrate	X	X	X	X	X
Microbiological quality	X	-	-	-	X

The results were set forth in the following Tables 7 and 8.

Table 6

(composition of Example 1)

Test	Beginning	3 months	6 months	12 months	18 months
pH	5.12	5.16	5.12	5.10	5.08
Desmopressin acetate hydrate	108.3%	104.4%	100.8%	98.9%	93.0%
Microbiological quality	Sterile	-	-	-	Sterile

Table 7

(composition of Example 2)

Test	Beginning	3 months	6 months	12 months	18 months
pH	4.00	3.98	3.98	3.95	3.97
Desmopressin acetate hydrate	109.0%	105.8%	100.1%	96.9%	92.5%
Microbiological quality	Sterile	-	-	-	Sterile

The results of the tables above show how the compositions of the present invention, though free from the preservatives deemed necessary by the prior art, anyway reveal to be stable in that concerns the active principle both at low temperature (5°C) and at room temperature (25°C).

CLAIMS

1. Pharmaceutical composition containing a therapeutically effective amount of a small or medium sized peptide in aqueous solution, characterized in that it is free from preservatives.
2. Composition according to claim 1 wherein the peptide is selected from the group consisting of derivatives and analogues of oxitocin and vasopressin, and the salts thereof.
3. Composition according to claim 2 wherein the peptide is selected from the group consisting of the analogues of vasopressin, and the salts thereof.
4. Composition according to claim 3 wherein the analogue of vasopressin is desmopressin acetate hydrate.
5. Composition according to claim 1 having a pH comprised between 3.5 and 6.
6. Composition according to claim 5 containing a buffer selected from the group consisting of citric acid/disodium phosphate dihydrate and citric acid/trisodium citrate dihydrate.
7. Composition according to claim 1 containing an agent for controlling the osmolarity.
8. Composition according to claim 7 wherein the agent for controlling the osmolarity is sodium chloride.
9. Composition according to claim 1 containing at least 0.02 mg of desmopressin, at least 3 mg of a buffer, an amount of an agent for controlling the osmolarity such that the osmolarity is kept at the physiologic values of the human plasma, and 1 ml of purified water.
10. Composition according to claim 9 containing from 3 to 6 mg of citric acid/disodium phosphate dihydrate buffer, or from 5 to 11 mg of citric acid/trisodium citrate dihydrate buffer.
11. Composition according to claim 9 containing from 0.02 to 0.15 mg of desmopressin, from 1 to 2.5 mg of citric acid monohydrate, from 2 to 5 mg of disodium phosphate dihydrate, 1 ml of water and an amount of sodium chloride such that the osmolarity is kept at the physiologic values of the human plasma.
12. Composition according to claim 1 containing 0.1 mg of desmopressin, 1.7 mg of citric acid monohydrate, 3 mg of disodium phosphate dihydrate, 1 ml of

water and an amount of sodium chloride such that the osmolarity is kept at the physiologic values of the human plasma.

13. Process for preparing the composition according to claim 1 comprising operating in pre-sterile environment, sterilely filtrating through 0,22 μm filters, collecting the filtrate in sterile environment and distributing it in sterile vials.

14. Spray unit containing a composition according to claim 1, and equipped with a multidose pump, absolute filter for the aspiration air, and an auto-blocking mechanism of the actuator.

15. Spray unit according to claim 14 wherein the vial is of glass.

PHARMACEUTICAL COMPOSITION CONTAINING A SMALL OR MEDIUM SIZED PEPTIDE

ABSTRACT

Pharmaceutical compositions containing a small or medium sized peptide, free from preservatives and stable before and during the use.